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George A. Frank
DRINKER BIDDLE & REATH LLP
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103-6996

EXAMINER	
ASHEN, JON BENJAMIN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,183	GEWIRTZ, ALAN	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,7-9,11,14 and 17-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7-9,11,14 and 17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Claims 1, 2, 5, 7-9, 11, 14, and 17-22 are pending in this application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 14 and 22 and claims 2, 5, 7-9, 11 and 17-21, which depend directly or indirectly from claims 1 or 14, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1, 14 and 22 are all drawn to methods of disrupting target gene expression using RNA interference wherein the method is practiced using an RNA that is "homologous" to a target gene (claims 1, 14) or a portion of a target gene (claim 22). The instant claims are drawn to a broad genus of RNA's that are homologous to any target gene or a portion of a target gene, wherein the presence of the RNA in a cell disrupts target gene expression. In the instant case, the breadth of the claimed genus

of an RNA that is homologous to any target gene or a portion of any target gene as claimed, is extremely broad and reads on a vast number of RNA species. The specification as filed discloses limited examples of specific RNA species that will function in the method as claimed and fails to provide any disclosure of sufficiently detailed, relevant identifying characteristics the claimed genus of any RNA that is homologous to any target gene or portion of any target gene which would provide evidence that applicant was in possession of the claimed invention. In particular, no adequate written description is provided of an RNA that is homologous to any target gene, or any portion of any target gene, that will disrupt the expression of any target gene because the specification does not provide the specific structure of an RNA that would correspond with the function of being homologous to any target gene.

This is particularly evident when considering the disclosure of the specification, which a) does not provide specific guidance concerning what level of nucleotide sequence homology is required of an RNA of the instant invention, that would correspond with the function of disrupting the expression of any target gene as claimed or b) provide the structure of an RNA that would correspond with the function of targeting any gene. In regards to homologous, the specification as filed provides no limiting language as to what level of homology is required to practice the method of the instant invention. Therefore, a vast number of RNA species reads on these claims. In light of this interpretation, what is the specific structure of an RNA that is homologous to any target gene or a portion of any target gene that would correspond with the function as claimed, of disrupting the expression of said target gene, for example?

Vas-Cath Inc. v. Mahurkar, 19USPQ2nd 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed (see page 1117). Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that

applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. > Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613.<

Therefore, Applicant has not provided adequate written description of their invention because Applicant has not shown how their invention was "ready for patenting" such as by the disclosure of the structure of RNAs that are homologous to any target gene, for example, that show that the claimed invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of any particular species of RNA that is homologous to any target gene, especially when the degree of homology that this RNA must share with said target gene is not defined and cannot be determined from the specification.

4. Claims 14, and 17-20 are maintained as rejected and claims 1, 5, 7, 9 and 11 and newly added claims 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in the prior Office action of 2/13/04. Amended claims 1, 2, 5, 7, 9 and 11 and newly added claims 21 and 22 are broadly drawn and read on both *in vitro* and *in vivo* methods. It is noted herein that the instant specification, while not being enabling for methods of using RNAi to disrupt gene expression *in vivo*, is enabling for the specifically disclosed embodiment of using RNAi *in vitro*, to practice methods of disrupting KitR gene expression in human cancer cell lines using KdsRNA. Therefore, amended claims 1, 2, 5, 7, 9 and 11 and

newly added claims 21 and 22 are maintained as rejected for the reasons of record as set forth in the prior Office action because these claims read on *in vivo* methods.

Response to Arguments

5. Applicant's arguments, filed 7/15/04, with respect to the rejection of record of claims 15-16 under 35 U.S.C 112 1st paragraph as failing to comply with the enablement requirement have been fully considered but are moot in view of Applicant's cancellation of these claims in the communication of 7/15/04. Applicant's arguments, filed 7/15/04, with respect to the rejection of record of claims 14 and 17-20 under 35 U.S.C 112 1st paragraph as failing to comply with the enablement requirement have been fully considered but are not found persuasive for the following reasons:

Applicant argues, on page 8, 2nd paragraph of the communication filed 7/15/2004, that the specification clearly and extensively teaches how to make dsRNA for administration to a human subject and that the dsRNA can be used to treat human RNA-based diseases or disorders, particularly cancer. Applicant points to pages 9-11 of the specification as filed for support of this assertion. In the instant case, counter to applicant's assertion, the specification as filed, does not teach one of ordinary skill in the art how to make and use the instant invention, but rather, simply asserts that the method of the instant invention, that requires administration of dsRNA (or pharmaceutical compositions of dsRNA) for the treatment human disease, can be practiced by any mode, conventionally known examples of which can be found in the art. However, as set forth in the prior Office action of 2/13/04 with reference to Agrawal

et al. 2000, Branch 1998, Green et al. 2000 and Jen et al. 2000, the state of the prior art taken as whole indicates that at the time of filing, one of skill in the art of RNAi would still require specific guidance to practice the claimed methods *in vivo*, particularly in regards to specific delivery of particular nucleic acids to effect a particular therapeutic outcome, as claimed. Therefore, applicant has not overcome the rejection of record because applicant has not pointed with any particularity, to where the necessary specific guidance is to be found in the specification as filed such that the method as claimed was enabled, despite the art recognized unpredictability of nucleic acid therapeutics in general and of RNA interference in particular.

Applicant points out, on page 9, line 3, that the mechanisms by which single stranded antisense oligodeoxynucleotides and dsRNA disrupt gene expression differ greatly and that the method of the instant invention is not antisense technology (pg 9, line 24) but that "However, as both antisense and RNAi methods require the delivery of nucleic acids to target cells, the teachings of the antisense art with regard to nucleic acid delivery have relevance to the claimed RNAi methods" (pg 9, lines 25-27). Applicant then argues on page 10, 2nd paragraph, that because delivery techniques for nucleic acid based therapeutic agents are well known in the art, such techniques need not be disclosed in detail. However, contrary to applicant's assertion, consideration of the prior art as a whole, with particular reference to Agrawal et al. 2000, Branch 1998, Green et al. 2000 and Jen et al. 2000 as set forth above and as set forth in the prior Office action of record, considers that the uptake and biological activity observed *in vitro* does not predictably translate to *in vivo* results, in part, at least, because formulations

and techniques for delivery *in vitro* are often not applicable *in vivo* (Jen et al. as set forth in the prior Office action). Therefore, applicant has not overcome the rejection of record because applicant has not pointed with any particularity, to an enabling disclosure in their specification which would overcome the art recognized unpredictability of delivery of nucleic acid therapeutics in general and of RNA interference in particular, to provide the desired therapeutic outcome *in vivo*.

In paragraph 2, page 10, Applicant contends that in the unpredictable arts, some experimentation may be required to identify compounds and methods which fall within the scope of the claims but that as long as the experimentation does not require ingenuity beyond that to be expected of one of ordinary skill in the art the experimentation is not undue and that, "Once presented with the teachings of the instant application, that one skilled in the art could practice the claimed RNAi method without undue experimentation (pg. 11, end of paragraph 2). However, contrary to Applicant's assertion, the art of RNAi, (as set forth in the prior Office action of record and the prior art references cited therein), was at the time of filing, and remains to this day, unpredictable, particularly in regards to the delivery of nucleic acid therapy *in vivo*. Applicant has not pointed out with any particularity, where specific guidance can be found in the instant specification that would enable practice of the claimed methods *in vivo*, to provide a particular therapeutic outcome in a mammal (or human). Therefore, this argument is not persuasive, as it does not overcome the prior grounds of rejection.

Applicant contends that zebra fish, are of course, not humans and that the zebra fish embryo RNAi experiments discussed in the rejection of record in regards to Oates

et al. and Wianny et al. are not relevant or predictive of human systems (pg. 12, 3rd paragraph). It is noted herein that applicant's claims are not drawn to zebra fish. However, in regards to the general unpredictability of *in vivo* RNAi treatment, Applicant has not pointed out, with any particularity, where specific guidance can be found in the instant specification that would enable practice of the claimed methods *in vivo*, to provide a particular therapeutic outcome in a mammal (or human). Therefore, this argument is not considered persuasive.

Applicant also argues that the conclusions drawn from studies on frog cells have little bearing on human cells (pg. 12, 4th paragraph). Applicant is correct in making this assertion, but, in making this assertion, applicant is essentially conceding that RNAi results, even *in vitro*, are unpredictable, and cannot be applied one species to another.

Applicant argues that they have demonstrated, for the first time, that RNAi can be induced in human cells and that one could not predict from mouse experiments that human RNAi could be reliably performed and that once demonstrated, one of skill in the art would not dismiss the claimed RNAi method as a therapeutic tool because of Wianny et al. (pg. 13, 2nd paragraph). It is noted herein that Applicant has indeed demonstrated that RNAi can be induced in human cells *in vitro* (as also acknowledged above). However, applicant has not provided an enabling disclosure of RNAi *in vivo*. Applicant's assertion that one of skill in the art would not dismiss the claimed RNAi method as a therapeutic tool because of Wianny et al. is moot because, as set forth above, the unpredictability of RNAi treatment *in vivo*, to achieve a particular therapeutic

outcome in a mammal (human), is taught by the state of the art as a whole. This unpredictability need not be taught by any one particular reference taken alone.

Applicant further contends that the transient nature of RNAi would not cause one of ordinary skill in the art to doubt the therapeutic effectiveness of agents that induce RNAi (pg. 13, 4th paragraph). This point is considered moot because, as set forth in the prior Office action (pg. 9, 1st paragraph), the rejection of record considers that the major impediment to using RNA interference as a therapeutic is that gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes. Applicant may be correct in their assertion that the transient nature of RNAi would not cause one of ordinary skill in the art to doubt the therapeutic effectiveness of agents that induce RNAi. However, Applicant has not overcome the rejection of record that considers that the *in vivo* delivery methods know in the state of the art at the time of filing were not effective for therapeutic purposes. Applicant has still not pointed out, with any particularity, where specific guidance can be found in the instant specification that would enable practice of the claimed methods *in vivo*, particularly in regards to delivery, so as to provide a particular therapeutic outcome in a mammal (or human).

Applicant contends that the present specification demonstrates the feasibility of inducing gene-specific RNAi in human cells with dsRNA without apparent interference from the PKR response (pg. 14, 2nd paragraph). However, this argument is considered moot because, as set forth previously in this action, Applicant has indeed demonstrated that RNAi can be induced in human cells *in vitro*. However, applicant has not addressed how their demonstration of RNAi *in vitro*, overcomes the rejection of record

which considers that the specification as filed lacks specific guidance that would enable practice of the claimed methods *in vivo*, particularly in regards to delivery, so as to provide a particular therapeutic outcome in a mammal (or human).

Applicant also argues that one skilled in the art would view Lyn kinase as a viable target for an anticancer therapeutic (pg 15, 1st paragraph). This argument is moot as it does not address the rejection of record which considers that the specification as filed lacks specific guidance that would enable practice of the claimed methods *in vivo*, particularly in regards to delivery, so as to provide a particular therapeutic outcome in a mammal (or human).

Applicant also argues that the RNAi-induced inhibition of KitR expression, with the concomitant reduction in the ability of Lyn kinase to autophosphorylate, therefore demonstrates that the claimed RNAi method has a therapeutic effect in human cells (pg. 15, 2nd paragraph). This argument is considered moot because as noted previously, Applicant has indeed demonstrated that RNAi can be induced in human cells *in vitro*. However, applicant has not addressed, how their demonstration of RNAi *in vitro* overcomes the rejection of record which considers that the specification as filed lacks specific guidance that would enable practice of the claimed methods *in vivo*, particularly in regards to delivery, so as to provide a particular therapeutic outcome in a mammal (or human).

Applicant also argues that the present specification (including the working examples) contains ample direction on how to practice the full breadth of the claimed therapeutic method (pg. 15, 4th paragraph). However, despite applicant's contention, for

the reasons set forth above and in the prior Office action of 2/13/04, the specification taken as a whole does not provide the specific guidance that would be required to enable one of skill in the art to practice of the claimed methods *in vivo*, particularly in regards to delivery, so as to provide a particular therapeutic outcome in a mammal (or human).

Applicant argues that although antisense and RNAi therapies do both involve the administration of nucleic acids, the two techniques vary so significantly in their mechanism of action that none of the impediments to antisense technology identified by the Examiner apply to the claimed RNAi method (pg 16, 1st paragraph) and that the problem of target site accessibility encountered in antisense techniques is, therefore, not present in the claimed RNAi method. However, as stated by applicant on page 9 of the communication filed 7/15/04, "as both antisense and RNAi methods require the delivery of nucleic acids to target cells, the teachings of the antisense art with regard to nucleic acid delivery have relevance to the claimed RNAi methods" (pg. 16, 2nd paragraph). Therefore, by applicant's own assertion, at least one impediment (said impediment being the art recognized unpredictability of *in vivo* delivery of a therapeutic nucleic acid) to antisense technology identified by the Examiner, applies to the claimed RNAi method. Therefore, applicant's argument is not persuasive because while the problem of target site accessibility encountered in antisense techniques may not be present in the claimed RNAi method, the rejection of record considers that the specification as filed lacks disclosure of the specific guidance required to enable one of skill in the art to practice of the claimed methods *in vivo*, particularly in regards to *in vivo*

delivery of a therapeutic nucleic acid, so as to provide a particular therapeutic outcome in a mammal (or human).

Applicant also argues that the present specification shows that RNAi can be induced in human cells without apparent interference from the PKR response and that therefore, one of skill in the art would not consider the induction of non-specific or non-antisense effects by antisense oligonucleotides to be relevant to the claimed RNAi method. This argument is considered moot because as noted previously, Applicant has indeed demonstrated that RNAi can be induced in human cells *in vitro* but has not indicated how the lack of induction of non-specific or non-antisense effects of methods of inducing RNAi *in vitro* overcomes the art recognized unpredictability of methods of inducing RNAi *in vivo*. Applicant has not shown, with any particularity, how their demonstration of RNAi *in vitro* overcomes the rejection of record which considers that the specification as filed lacks specific guidance that would enable practice of the claimed methods *in vivo*, particularly in regards to delivery, so as to provide a particular therapeutic outcome in a mammal (or human).

Applicant further contends that only a few molecules of dsRNA need be delivered to a target cell in order to significantly inhibit gene expression through RNAi and that the problem of delivering sufficient amounts of material to a cell in order to produce the desired inhibition of gene expression encountered in antisense therapies is therefore not present in the claimed RNAi methods (pg. 17, 3rd paragraph). This argument is considered moot because as noted previously, Applicant has indeed demonstrated that RNAi can be induced in human cells *in vitro* but has not indicated how the problem of

delivering sufficient amounts of material to a cell, *in vivo*, in order to provide a particular therapeutic effect has been overcome in light of the art recognized unpredictability of *in vivo* delivery of nucleic acid therapeutics, as set forth previously in this Office action and in the prior Office action of 2/13/04.

Applicant also asserts that no specific reasoning has been given refuting that one skilled in the art would accept the *in vitro* human cancer cell data shown in the present specification as reasonably predictive of a therapeutic effect *in vivo*. However, contrary to this assertion, Applicant's attention is drawn to page 11 of the prior Office action wherein the Examiner has provided the specific reasoning that the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results due to differences in the physiological conditions of a cell *in vitro* and *in vivo*.

Applicant also argues that because human cancer cell lines have long been used as models of *in vivo* disease, and one skilled in the art would accept that there is a reasonable correlation between the disclosed *in vitro* utility and the claimed *in vivo* activity of the dsRNA and that therefore, a rigorous correlation between the *in vitro* model and the *in vivo* activity as claimed is not necessary for enablement nor is it possible prior to FDA approval of a dsRNA-based therapeutic. However, contrary to Applicant's contention, given the art recognized unpredictability of *in vivo* delivery of nucleic acid therapeutics, as set forth previously in this Office action and in the prior Office action of 2/13/04, one skilled in the art would recognize that for any particular therapeutic for any particular disease, a rigorous correlation between an *in vitro* model of that disease and the *in vivo* activity of a claimed nucleic acid therapeutic for treatment

of said particular disease would be required to enable one skilled in the art to make and use the instant invention as claimed. Applicants argument in regards to enablement not being possible prior to FDA approval of a dsRNA-based therapeutic, is considered spurious because the state of the art of nucleic acid therapies considers ex vivo treatment of art recognized animal models of particular diseases to be enabling.

Therefore, for all of the reasons set forth above and in the prior Office action of 2/13/04, claims 14, and 17-20 are maintained as rejected and claims 1, 5, 7, 9 and 11 and newly added claims 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Response to Arguments

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. Applicant's arguments, see pages 5-7, filed 7/15/04, with respect to rejection of record under 35 U.S.C 112 2nd paragraph, of claims 1, 5, 9, 11, 14 and 17-20 as being indefinite, have been fully considered and are persuasive. Additionally, Applicant's arguments with respect to claims 3-4, 6, 10, 12-13, and 15-16 have been considered but are moot in view of Applicant's cancellation of these claims in the communication filed 7/15/04. Therefore, in light of the above, the rejection of record in regards to claims 1, 5, 9, 11, 14 and 17-20, as being indefinite, has been withdrawn.

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1, 2, 5, 7-9, 11 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Fire et al. (U.S. Patent 6,506, 559). Fire et al. disclose a method for inhibiting expression of a target gene using double stranded RNA to induce RNAi in a cell *in vitro* (Column 26, claim 1) wherein the cell is from an animal (Column 26, claim 6). Fire et al. disclose that the cell with the target gene may be derived from or contained in any organism (column 8, line 13-14) and that examples of vertebrate animals include mammals and human (column 8, lines 35-37) and that the cell having the target gene may be "immortalized or transformed, or the like" (column 8, lines 52-55) and that "the present invention could be used for treatment or development of treatments for cancers of any type, including solid tumors and leukemias..." (Column 10, lines 26-28). Fire et al. disclose that lipid mediated carrier transport can be used to introduce nucleic acids to cells (Column 9, lines 55-60). Fire et al. also disclose that inhibition of gene expression refers to the absence (or observable decrease) in the level of protein and/or mRNA product from a target gene (Column 6, lines 55-57), thereby indicating disruption of gene function (which is to produce protein).

Therefore, Fire et al. disclose each and every aspect of the instant claims.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jba